REMARKS

Applicant's attorney wishes to thank the Examiner for the careful consideration given to the present application. Currently, claims 1-26 have been canceled and new claims 27-35 have been added. Support for the new claims and amendments can be found in the specification as filed. Thus, no new matter has been added. Applicant addresses each of the rejections set forth in the Office Action in the order presented therein.

35 U.S.C. § 112

The Examiner has rejected claim 25 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant has canceled claim 25 and has indicated new claims 34 and 35 that recite the therapeutically effective amount of the chimeric protein is achieved in the plasma. Support for the new claims can be found in the specification as filed, for example, page 16 - lines 14-22, and thus no new mater is added. Accordingly, reconsideration and withdrawal of the Examiner's rejection is respectfully requested.

35 U.S.C. § 103(a)

Claims 1-3, 5, 9, 10, 22, 25, 26 are rejected under 35 U.S.C. § 103(a) as being obvious over Olsen (WO 00/64482) in view of either Yick or Zuo. Applicant respectfully disagrees.

Olsen discloses an "amphibody" comprised of at least two components, wherein the first component, the "anti-end," is antibody-based. This anti-end is capable of locating, binding to inhibitory molecules in a tissue environment. The second part of the amphibody, the pro-end, will, in that particular environment, simultaneously and present a growth stimulating substance to the regenerating axon **in the location of the previously exposed inhibitory site**. *see P. 4.* Accordingly, Olsen discloses that the first component is an antibody or fragment thereof that localizes and binds to neural inhibitory molecules that are expressed on target cells such as glial cells, neurons, fibroblasts, blood cells or extracellular matrices. *see P7, lines 13-30.*

Each of Yick and Zuo, at most, teach that chondroitin proteoglycans are extracellular matrix components which inhibit neural growth and regeneration following injury.

By way of contrast, Applicant's claimed invention comprises a chimeric protein comprising two polypeptide sequences wherein the first polypeptide sequence is an enzymatic moiety and the second sequence is a peptide with regenerating activity. Of note for the present rejection is the enzymatic moiety (first peptide sequence) of the claimed invention; this enzymatic moiety is selected from the group consisting of chondroitinases, hyaluronidases, and matrix metalloproteinases. In contrast to the "anti-end" of the Olson amphibody, these enzymatic moieties do not specifically bind and sequester an inhibitory antigen converting an inhibitory site into a stimulatory one .

Rather, these chondroitinases, hyaluronidases, and matrix metalloproteinases are known enzymes that destroy proteoglycans. Enzymatic moieties exert their function by converting a substrate to a different molecule, i.e., a product. The structure, concentration and physical and chemical properties of the substrate and product varies immensely. It is well-settled that 1) a proposed modification cannot render the prior art unsatisfactory for its intended purpose and 2) that a proposed modification cannot change the principle of operation of a reference. Changing out the specific binding "anti-end" of Olson for an enzyme would destroy the intended function of the Olson amphibody.

MPEP expressly states that "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP 2143.01.(v) Further, the MPEP states that "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." MPEP 2143.01.(vi)

The primary reference in this case, Olson, discloses an amphibody wherein the first component is an antibody that binds directly to a proteoglycan on the spot and thus hindering the proteoglycan and turning an inhibitory spot to a stimulatory spot wherein the second component of the amphibody expresses positive modulators of axonal growth, precisely

on the spot of the previously exposed inhibitory site in a "sugarcoat" fashion *see* p 19, Lines 5-15. Olson fails to disclose that the first component could be an enzymatic moiety, particularly, chondroitinases, hyaluronidases, and matrix metalloproteinases. The Office appears to suggest that it would be obvious to substitute the first component of Olson's amphibody, which is an antibody, with chondroitinases, hyaluronidases, and matrix metalloproteinases.

However, the Office's position of modifying Olson's amphibody by substituting the antibody component of the amphibody with an enzymatic moiety such as chondroitinases, hyaluronidases, and matrix metalloproteinases is improper because it renders the prior art amphibody unsatisfactory for its intended purpose. The amphibody exerts its effect by the fact that the first component, which is an antibody, inhibits the activity of the target without necessarily destroying the target, and then the second component, which is neurotrophic, can stimulate neurite regeneration and elongation. In contrast, chondroitinases, hyaluronidases, and matrix metalloproteinases are enzymes that destroy the target proteoglycans and modify them to completely different compound(s) and that are localized at the site of the enzymatic reaction. Thus, the milieu of an antibody reaction and an enzymatic reaction are significantly different.

Substituting the prior art amphibody's first component with chondroitinases, hyaluronidases, or matrix metalloproteinases would destroy the amphibody's ability to inhibit the function of proteoglycans by hindering them while keeping their structure intact and further results in the destruction of the target proteoglycans, and not merely inhibition of the proteoglycans through use of an antibody. Therefore, as instructed by the case law and MPEP 2143.01, it is improper for the Office to take the position that it would have been obvious to one skilled in the art that the antibody component of Olson could be substituted with an enzymatic component, since the enzymatic moiety would destroy the intended function of the prior art amphibody.

Further, one skilled in the art would have no reasonable expectation of success that a chimeric protein comprising a first polypeptide selected from the group consisting of chondroitinases, hyaluronidases, and matrix metalloproteinases; and a second polypeptide possessing regenerating activity for neural cells as claimed by Applicant would exhibit the

requisite activity based upon the teachings of Olson, Yick and/or Zuo, because Olson merely teaches that the proteoglycan activity is to be inhibited through use of an antibody, which does not change the milieu. There is simply no teaching or suggestion that using an enzymatic moiety, such as chondroitinases, hyaluronidases, or matrix metalloproteinases, that destroys the proteoglycan and significantly changes the milieu, would otherwise result in axonal growth when combined with the second component of Olson's amphibody.

Furthermore, the use of enzymatic removal of carbohydrate chains from CSPGs is not essentially the same as blocking their inhibitory activity as suggested by the Office.

Prior to the present invention, in the context of Olson, the regenerating neurons are growing over an environment of natural CSPGs covered with antibody. In the present invention, the environment that the neurons must traverse is actually degraded, and there is no way to anticipate from Olsen that enhanced regeneration would function at all. Following cleavage of the carbohydrate chains of the CSPGs, as described in the present invention, the neurons must regenerate across an environment comprising proteoglycans with short chains (one, two and three carbohydrates) known as 'stubs'. These stubs are completely unique to chondroitinase digestion and do not occur naturally. Growth and regeneration across these stub-laden proteoglycans can not be inferred or anticipated from Olsen et al.

Moreover, as stated in the prior submissions, at the time of the present invention (and even after as noted below) proteoglycans were understood to have important roles in normal physiology. For example, Grumet et al Perspect Dev Neurobiol 1996; 3(4):319-330 (abstract) notes that differential expression of proteoglycans may be important for modulating cell adhesion as well as axonal growth and guidance during development; notably, the continued expression of these molecules may prevent these processes from occurring unfettered in normal adult tissue.

Additionally, proteoglycans are known to be components of the perineuronal net. The perineuronal net could provide recognition molecules between certain neurons and their surrounding cells, and participate in the selection and consolidation of their relationship. (*See,*

e.g., Celio and Blumcke "perineuronal nets - a specialized form of extracellular matrix in the adult nervous system" Brain Res Brain Res Rev, 1994 Jan; 19(1):128-45) (abstract).

Even after the filing date, proteoglycans were understood to have important roles in the structure and healing of the adult nervous system. Rhodes and Fawcett J. Anat (2004) 204:33-48 at page 39 indicate that proteoglycans surrounding damaged tissue and disrupted blood brain barrier have a vital role is sealing off a lesioned area and that the proteoglycans may limit cavitation and secondary injury. Of note, it is suggested that if upregulation of proteoglycans were prevented that this might have "detrimental effects on the healing and sealing processes." Id.

Accordingly, degrading proteoglycans, prior to the findings of the present invention, would have been expected to have deleterious consequences, and would not be an obvious research choice. Again, neutralizing or suppressing proteoglycans of interest is far different than degrading and destroying them. Applicant was first to identify chimeric proteins for promoting repair and regeneration of neurons with the first component specifically capable of destroying proteoglycans.

Yick, Zuo and Gearing fail to cure the deficiencies of Olsen. Therefore, for at least the reasons set forth above, Applicant submits that the pending claims are not obvious over Olsen in view of Yick, Zuo and Gearing. Accordingly, reconsideration and withdrawal of the Examiner's rejection is respectfully requested.

CONCLUSION

Applicant believes that the claims as presented are in condition for allowance, and notice to such effect is respectfully requested. Should the Examiner have any questions or comments, or need any additional information from Applicant's attorney, the Examiner is urged to contact the undersigned.

Applicant has timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 500436.

Respectfully submitted,
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